Opioid Pharmacokinetics, Serum Predictability, and Expected Metabolites

DRUG	Half-Life (Hrs[A])	Time to Steady State (Hrs[A])	Metabolites	Time to Peak Conc. (Hrs[A])	Serum Predict-ability	Bioavailability	Serum Concentration (ng/mL)
BUPRENORPHINE / NALOXONE[44,45,46] (Suboxone)	24-42/2-12	120-294	Norbuprenorphine	1.53-1.72 / 0.77-0.81	Y	15% / 3%	8/2mg: 3.37+/-1.8 and 0.193+/-0.0912
TRANSDERMAL BUPRENORPHINE[48]	26	3 days	Norbuprenorphine	60	Y	15%	Mult. Dose: Single Dose: 10mcg/hr: 0.224 5mcg/hr: 0.176 10mcg/hr: 0.191 20mcg/hr: 0.471
BUCCAL BUPRENORPHINE[48,49]	27.6+/-11.2	3 days	Norbuprenorphine	2.5-3	Y	46-65%	Mult. Dose: Single Dose: 60mcg q12h: 0.077+/-0.020 75mcg: 0.17+/-0.30 120mcg q12h: 0.156+/-0.044 300mcg: 0.47+/-0.47 180mcg q12h: 0.216+/-0.106 1200mcg: 1.43+/-0.45 240mcg q12h: 0.364+/-0.125
CODEINE [13,14,24]	2.5-3.5	12.5-17.5	Morphine, Norcodeine, Normorphine, Hydrocodone, Codeine 6-glucuronide	1-2	Y	Well absorbed	IR 180mg = 222.9 +/- 48.9
TRANSDERMAL FENTANYL [7,8,9,24]	16-25	72	Norfentanyl, 4-N-(N-propionylanilino) piperidine, 4-N-(N-hydroxypropionylanilino) piperidine, 1-(2-phenethyl)-4-N-(N-hydroxypropionylanilino) piperidine	24-72	Y	92%	25 mcg/hr = 0.6 +/-0.3 50mcg/hr = 1.4 +/- 0.5 75mcg/hr = 1.7 +/- 0.7 100mcg/hr = 2.5 +/- 1.2
TRANSBUCCAL, TRANSMUCOSAL SUBLINGUAL FENTANYL[7]**	14-19 (Onsolis) 2.6-11.7 (Fentora) 7 (Actiq) 5-13 (Abstral)	13-98	As above	0.75-4 (Onsolis) 0.58-0.78 (Fentora) 0.3-2 (Actiq) 0.25-1 (Abstral)	Y	Onsolis 71% Fentora 65% Actiq 47% Abstral 54%	800 mcg = 1.67* (Onsalis) 800 mcg = 1.59* (Fentora) 800 mcg = 1.03* (Actiq) 800 mcg = 1.42* (Abstral)
HYDROCODONE[15,16,17,24, 39,40,41]	3.8	19-22.5	Hydromorphone, Norcodeine, 6-beta-hydrocodol, 6-alpha-hydrocodol, 6-beta-hydromorphol, 6-alpha-hydromorphol, norhydrocodone	1.3	Y	Well absorbed	IR 10mg = 23.6ng +/-5.2
HEROIN [21,22,23,24]	~3 min. 1.7-5.3 min	~15 min.	6-acetylmorphine, Morphine, Morphine-3-glucuronide, Normorphine, 6-acetylmorphine 3-glucuronide, Normorphine glucuronide	10 minutes for I.M. dose[B]	Y	Diacetylmorphine undergoes complete presystemic metabolism to morphine after oral administration	112mcg/min for 5 min Heroin level = 57 ng/mL[C] 6-acetylmorphine level=15ng/mL[C]
HYDROMORPHONE [10,11,12,24]	2.5	12.5	Hydromorphone-3-glucuronide, Hydromorphone-3-glucoside, Dihydroisomorphine-6-glucuronide, Dihydroisomorphine-6-glucoside, Dihydroisomorphine, Dihrydromorphine[E]	48-60 min.	Y	24%	IR 48 mg = 19.7 +/- 4.04
LEVORPHANOL	1 dose: 11-16 Chronic: 30	72	3-glucuronide	approximately 1	?		
MEPERIDINE	~3.6	3-6 days	Normeperidine, meperidinic acid, normeperidinicacid	1-1.5	?	Variable: IM-57%	100 mg IM = 551 ng/mL
METHADONE [18,19,20,24]	24	~5 days	EDDP (2-ethyl-1,5-dimethyl-3,-3-diphenylpyrrolinium), EMDP (2-ethyl-5-methyl-3,3-diphenylpyraline)	2-4	Y	85%	Linear drug levels increase 260ng/mL for every 1mg/kg consumed
MORPHINE [4,5,6,24,25,51] IR, CR (MS Contin)	2-4	24	Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, 7,8-dihydromorphinone, codeine (minor)	IR = 1 CR = 2-3	Y	20-40%	IR 15mg q6h: • Cmax: 22.0 ± 1.0 • Cmin: 3.5 CR (MS Contin) 30mg q12h: • Cmax: 20.3 ± 1.0 • Cmin: 4.5
MORPHINE / NALTREXONE[43] (Embeda)	29	145-203	As above + 6-beta-naltrexol	7.5	Y	20-40%	lower Cmax and a higher Cmin than conventional immediate-release morphine at steady-state

Developed by: Jeffrey Fudin, BS, PharmD, DAIPM, FCCP. FASHP
Rev 08-23-2017: Mena Raouf, PharmD

Morphine ER (Kadian)[52]	2-4	24	Morphine-3-glucuronide, Morphine-6-glucuronide, Normorphine, 7,8-dihydromorphinone, codeine (minor)	10.3 ± 3.3	Y	40%	100mg daily (steady-state) • Cmax: 37.3 ± 14.0 • Cmin: 9.9 ± 5.2
OXYCODONE [1,2,3,24,53] IR, CR (OxyContin)	IV,IR=3.2 CR=4.5-8	IR: 17.5 CR: 24-36	Noroxycodone, Oxymorphone, Oxycodyl, Oxymorphol, Noroxycodyl	IR: 1.6 CR: 2.1-3.2	Y	60-87%	IV (0.14 mg/kg)=34-38 IR 5mg q6h: • Cmax: 15.6 +/- 4.4 • Cmin: 6.5 +/- 3.1 CR (OxyContin) 10mg q12h: • Cmax: 15.1 +/- 4.7 • Cmin: 6.2 +/- 2.6 CR (OxyContin) 40mg q12h fasted • Cmax: 42.30 +/- 10.44 • Cmin: 14.1 +/- 3.48 CR (OxyContin) 40mg q12h with high fat meal • Cmax: 63.11 +/- 12.86 • Cmin: 15.8 +/- 3.13
OXYCODONE ER (XTAMPZA)[53]	Fasted: 14 hours Low fat meal: 8.75 Medium fat meal: 6.8 High fat meal: 5.6	24-70	Noroxycodone, Oxymorphone, Oxycodyl, Oxymorphol, Noroxycodyl	3-3.7 hours (Fasted, low-medium fat meal) 6.23 hours (high fat meal)	Y	Fasted: 75% Fed: 114%	36mg q12h: Fasted: 31.5 +/- 9.5 with low fat meal: 37.5 +/- 9.57 with medium fat meal: 58 +/- 18.9 with high fat meal: 51.85 +/- 14.362
OXYMORPHONE[42]	IR = 7.2 -9.4hr ER 9.4 – 11.3	IR: 3-4 days ER: 3 days	Oxyorphone-3-glucuronide, 6-OH-oxymorphone	IR: 30mins ER: 3 hrs	Y	10%[F]	IR 20mg: 4.39 +/-1.72 ER 20mg: 2.54 +/-1.35
TAPENTADOL[47, 54]	IR : 4 ER: 5.2 +/- 1.0	20-28	Tapentadol-O-glucoronide, desmethyl tapentadol, hydroxyl tapentadol	IR: 1.25-1.5 ER: 5	Y	32%	IR 50mg single dose: • Cmax: 54.6 +/- 19.6 • Cmin: 27.3 +/- 9.9 100mg q6h • Cmax: 118 +/- 33.1 • Cmin: 59 +/- 16.6 ER single-dose: • 50mg: 10.1 +/- 2.59 • 100mg: 25.5 + 6.38 • 200mg: 62.5 +/- 17.9 • 250mg: 89.3 +/- 28.1 ER multiple dose • 250mg q12h: 132 +/- 35.1
TRAMADOL (M1 metabolite)[50]	IR: 5.6-6.7 (6.7-7) ER: 6.5-10 (7.5-11)	IR: 2 days ER: 4 days	O-desmethyltramadol (M1)	IR: 1-2.3 (1.5-2.4) ER: 4-12 (5.15)	Y	IR: 75% ER: 85-95%	100mg IR q6h: 592 (110) 200mg ER qd: 332-345 (70-95)

Footnotes for Table Above

IR = Immediate Release Products, CR = Continuous Release products, SS = Steady State
A-Hours, unless otherwise indicated
B-Can detect heroin and 6-acetyl morphine within 10-15 minutes of parenteral administration
C-Administered IV in a single patient over 180 minutes
** These products are not considered bioequivalent
D-Cummulative amount of fentanyl release from patch dose in 24 hours.

E-hydromorphone is 7,8-dihydromorphinone: Please note that morphine metabolism to hydro-
morphone has been confirmed in 8 mammals other than humans. There is only data that correlates the conversion of morphine to hydromorphone in humans.[29]
F- the bioavailability of oxymorphone increases significantly in hepatically (up to 12 fold) and renally impaired (65% with creatinine clearance less than 30 ml/min) patients
*peak concentrations

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